IRW AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: David A. Edwards and Jeffrey S. Hrkach

Application No.: 09/383,054 Group: 1616

Filed: August 25, 1999 Examiner: Frank I. Choi

Confirmation No.: 6042

For: STABLE SPRAY-DRIED PROTEIN FORMULATIONS

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, or is being facsimile transmitted to the United States Patent and Trademark Office on:

Sept. 15, 2004 Judy Breen
Date Signature

Judy Breen

Typed or printed name of person signing certificate

SECOND SUPPLEMENTAL BRIEF ON APPEAL

Mail Stop Appeal Briefs Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Second Supplemental Brief, the third appeal brief filed in less than one year, is being filed pursuant to 37 CFR 1.192 and in light of the recently received Office Action which reopened prosecution. This non-final Office action is the seventh action received by the Applicants in this case and adds new grounds of rejection against claims that are nearly identical to original claims. Clearly, the claims have been more than twice rejected and this Brief is timely. It is requested that the Office finally close prosecution on this case and either allow the claims or pass the application to the Board of Patent Appeals and Interferences. A transmittal letter and fee under 37 CFR 1.17(h) have been filed previously. The required sections under 37 CFR 1.192 are set forth below under separate headings.

(1) The Real Party of Interest

The real party of interest in this appeal is Advanced Inhalation Research, Inc. by virtue of the Assignment recorded on November 1, 1999 at Reel 010349 and frame 0126.

(2) Related Appeals and Interferences

There are no related appeals or interferences at this time known to the appellant, the assignee or its representative which will directly affect or be directly affected by or have a bearing in the Board's decision in the pending appeal.

(3) Status of the Claims

Claims 50, 52-69, 91, 93-108, and 128-131 are pending, finally rejected and appealed. Claims 1-49, 51, 70-90, 92 and 109-127 have been canceled.

(4) Status of the Amendments

An Amendment After Final Rejection was filed on May 19, 2003 and was entered on or about December 8, 2003.

(5) Summary of the Invention

The invention relates to methods for producing spray-dried particles having improved stability of a protein comprising the steps of combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and spray-drying the mixture to produce spray-dried particles comprising a stabilized protein (please note that the use of the word "comprising" here permits additional yet unnamed materials in the final product; to avoid any confusion, this should not be interpreted to mean that the product of the claim can contain any unnamed material as the entire claim must be read for proper construction, not phrases taken in isolation). All of the claims present further limitations that clearly define the components that make up the final product. In Claim 50, for example, the particles produced by the claimed method consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. In Claim 128, for example, the buffer salt is required.

(6) Issues

The issues now on appeal are whether the Examiner has established that the claims are indefinite and whether a prima facie case of obviousness over Durrani in view of Backstrom, Edwards and Remington's exists. It is believed that the Examiner's objection entitled Response to Amendment, as best as Applicants understand it, is moot in view of this submission.

(7) Grouping of Claims

Claims 53, 56, 57, 62-64, 94, 97, 98, 102-104 and 128-131 do not stand or fall together with the remaining claims.

(8) The Rejections under 35 U.S.C. 112, Second Paragraph

(a) The First Rejection

The Examiner rejects all claims under 35 USC 112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner states that the claim states that "the spray-dried particles comprising a stabilized protein", referring to paragraph (b) of Claim 50, for example, but subsequently requires the particles to "consist of the stabilized protein, phospholipid and, optionally, a buffer salt..." The Examiner then suggests some language that is, frankly, already present in the claims.

(b) The Rebuttal

The issue, although not articulated by the Examiner, is whether a claim is necessarily rendered indefinite by the use of two types of transitional phrases. Appellants argue that it is not. While it may be true that the phrase "comprising a stabilized protein" is redundant in the claim, it does not make the claim unclear or indefinite.

Referring to the long history of this application, original Claim 1 permitted the particles to possess unidentified components. This was accomplished by using the transitional phrase "comprising" in paragraph (b). Claims 2 and 3 narrowed the possible additional components of the particles adding "wherein" clauses that used transitional phrases "consisting essentially of" and "consisting of". Indeed, this is a common practice. These original claims were never considered indefinite or unclear by any previous Examiner. To avoid certain rejections made by

the previous Examiner and to narrow the issues for consideration, the limitations of Claim 2 (and, subsequently, Claim 3) were introduced, nearly verbatim, into Claim 1 and Claim 1 was renumbered as new Claim 50. The claim, in its structure, is no different from a dependent claim which further narrows a transitional phrase from that used in the claim from which it depends. For the same reasons that such a dependent claim is not indefinite, an independent claim so structured is not indefinite.

How should such an independent claim be construed? The claim should be construed in the same manner as the originally presented dependent claim. Claim 50 clearly and explicitly precludes additional components other than a stabilized protein, a phospholipid and an optional buffer salt. The transitional phrase in paragraph (b) is not inconsistent with the "wherein" clause. The particles as described in paragraph (b) indeed contain (and, thereby, "comprise") components not specifically listed there, i.e., a phospholipid and an optional buffer salt. The wherein clause limits the components of the particles to those listed therein. The claim, when read in its entirety, thus requires the particles produced by the process to "consist of the stabilized protein, the phospholipid and, optionally, the buffer salt." Particles which also contain added cholesterol or lactose are not embraced by this language.[1]

Of course, this rejection can be easily avoided by deleting the phrase "comprising a stabilized protein" in (b). However, (1) two Briefs have already been filed in an attempt to move this application to the Board of Appeals, (2) this third Brief is in response to the seventh Office action, (3) the action explicitly prohibits amendment with the Appeal, (4) the filing of an additional amendment at this stage obviously does not guarantee that yet another new ground of rejection will be added in the next Office action, and (5) appeal appears to be inevitable. Thus, an amendment at this stage, even if it clearly avoids a ground of rejection on appeal, appears to only guarantee an eighth Office action and additional delays and expense by the Applicants. Applicants regret placing such an easily avoidable issue before the Board for consideration. Nonetheless, reversal of the rejection is requested.

---

[1] Please note that, of course, residual solvent and contaminants inherent to the process will also be present; thus, this discussion should not be construed as absolutely prohibiting such inherent components.

(c) The Second Rejection

The Examiner rejects Claims 128-131 under 35 USC 112, second paragraph as "failing to set forth the subject matter which the applicant(s) regard as their invention." In a novel rejection, the Examiner has misinterpreted an argument in the Supplemental Brief at pages 7 and 8 and cites the argument as evidencing this new ground of rejection. In particular, the rejected claims recite "buffer salts". The prior art which, was the subject of the argument, referred to "phosphate salts," which is a buffer salt. The argument referred to "such salts," meaning phosphate salts and the like (i.e., buffer salts). The rejection states, in essence, that the argument evidences the Applicants' intent to limit the claims to "phosphate salts." As such, the Examiner concludes that the claims, directed to "buffer salts," are in violation of the recited statute.

In a second argument, the Examiner points to the Supplemental Brief, at page 8, which stated, with respect to an obviousness rejection made by the Examiner, that "there was no motivation to specifically choose the formulation to consist essentially of hGH...." The Examiner finds the claims (Claims 53 and 94?) confusing because the claims use the phrase "consist of" and the argument uses the phrase "consisting essentially of." In the alternative, referring to the opening statement of the rejection, the Examiner may be stating that the claims are not directed to the subject matter Applicants regard as their invention. It is assumed that the Examiner intended to reject Claims 53 and 94, rather than Claims 128-131 which is referenced in the opening sentence of the paragraph.

In any event, all of the claims are clear and are directed to that which Applicants regard as their invention. The rejection is clearly improper and should be withdrawn.

While the undersigned has experienced Examiner rebuttals asserting that an Applicants' argument was unconvincing for the scope of a particular claim, this is the first instance in my experience that such an argument has been used as *evidence* in a new ground of rejection under 35 USC 112, second paragraph, stating that the invention *must* be narrowed to the Examiner's understanding of the scope of an Applicant's argument. Further, this is the first instance in my experience that an argument, asserting that the final rejection as stated is wrong, has been used as *evidence* in a new ground of rejection stating that a narrower claim is confusing.

(d) The Rebuttal

It is noted, at the outset, that the claims, in fact, set forth the subject matter which the Applicants regard as their invention. No critical or essential limitations have been omitted. Applicants note that Claim 50 specifically recites that the buffer salt is optional. Claim 128 removes the word "optional." Claim 50 has, properly, not been rejected. It is exceedingly clear that Applicants regard as their invention both the embodiment where buffer salt is added (Claims 50 and 128) and where buffer salt is not (Claim 50). Further, the claims are consistent with the teachings of the specification as originally filed. The recitation of, and argumentation for, preferred embodiments (e.g., phosphate salts) that fall within the scope of the claims does not in anyway support a rejection on this ground. With respect to the second ground of rejection, the use of the transitional phrase "consisting of" is well recognized. The argument that a final rejection is wrong does not in anyway provide evidence that an amended and narrower claim is confusing. There is no reasonable basis for this rejection.

With respect to the second ground raised by the Examiner in this rejection, Applicants also request a reversal. The fact that the argument says that the rejection is improper (whether it be of the finally rejected claims, which used the transitional phrase "consisting essentially of," or of the narrower appealed claims, which use the transitional phrase "consist of") does not in any way render the scope of the amended claims confusing. The presentation and appeal of a narrower claim than that which was finally rejected and the argument that the final rejection is in error, does not in any way suggest that the subject matter of that claim is not directed to that which Applicants regard as their invention.

Of course, this rejection may also be easily avoided by limiting the buffer salts in Claims 128-131 to phosphate buffer salts and broadening the claims to "consisting essentially of". Given the scope of Claim 50, the former amendment would have a trivial impact upon the overall scope of any patent granted from this application. The latter amendment would simply reintroduce issues that the narrowing amendment was intended to avoid for the purposes of this appeal. However, Applicants' reticence to make any further amendments is explained above. Applicants again regret placing such trivial issues before the Board.

Arguments (1) with respect to preferred embodiments, (2) highlighting that the prior art teaches away, or (3) that the final rejection is wrong, do not offer a reasonable basis for a rejection asserting that a narrowed claim should be even narrower under 35 USC 112, second

paragraph or that a claim which is otherwise clear is confusing. The Examiner has not offered a single legal citation for this novel basis for the rejection. Reversal is requested.

(9) The Rejection under 35 USC 103

(a) The Rejection

All claims stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Durrani *et al.* ("Durrani) in view of Backstrom et al. (US Pat. 6,632,456), Edwards et al. (US Pat. 5,985,309) and Remington's. In support of the rejection the Examiner relies upon earlier Office actions, which state:

> Durrani discloses a process to directly spray dry a drug/lipid powder composition comprising preparing an aqueous solution containing a drug and a lipid containing ethanol solution. The mixture is then spray dried to get particles (p 40, claim 1). Durrani further teach that the drug may be selected from a group which includes insulin.... Durrani further teaches that the lipid may be selected from the group consisting of phosphatidylglycerol.... Lastly, Durrani teach that the diameter of the resulting particles is between 0.1 and 20 microns (p 14, l 30)....
>
> One of ordinary skill in the art would have been motivated to make a spray dried composition of a drug and a lipid based on the generic claim of Durrani. The expected result would be a stable spray dried powder formulation. Therefore, this invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Backstrom is stated to teach spray-dried pulmonary products that contain proteins and a phospholipid as an absorption enhancer. The Examiner states that many of the excipients used in Backstrom are said to be optional. Edwards is stated to teach pulmonary products with proteins and phospholipids having particular physical characteristics. Remington's is stated to teach that SEC and HPLC are known methods for identifying protein stability.

After the lengthy discussion of the content of these references, the Examiner states, at page 6 of the Office action, that "[t]he difference between the prior art and claimed invention is that the prior art does not expressly disclose methods of producing spray-dried particles... by combining protein, phospholipid, aqueous solvent and/or organic solvent, optionally, buffer salt, spray drying to form a particle consisting of a stabilized protein, phospholipid, optional buffer

salt wherein the phospholipid is at least about 10% wt." Please compare the quoted section and the claim. To rephrase the obligatory sentence which describes the difference between the claims and prior art, the Examiner states that "[t]he difference between the prior art and claimed invention is that the prior art does not expressly disclose [the claim]." The undersigned is at a loss as to how to respond, except that I am in agreement. The prior art does not disclose the claim and the rejection does not identify the difference between the prior art and the claim.

The Examiner goes on to state that "[h]owever, the prior art amply suggests the same as the prior art discloses spray-dried compositions for inhalation containing protein, phospholipid, aqueous and/or organic solvent and optional buffer salt and discloses that the amount of the phospholipid is at least about 10% by weight." This sentence appears to directly contradict the first sentence and only vaguely states that the invention is "suggested." Please note that the statement fails to consider the claim limitation that the particles "consist of" the stabilized protein, phospholipid and optional buffer salts. Certainly more is required to satisfy the Office's burden in making an obviousness rejection. Instead, the Examiner leaves it to the Applicants to identify the differences between the claimed invention and prior art and speculate how these references may be combined to arrive at the claimed invention. After seven office actions and reopening prosecution after two briefs on appeal, the Applicant is entitled to at least a statement of rejection that complies with the form of Graham v. John Deere. Nonetheless, Applicants disagree with the rejection and for purposes of completeness, offer the following rebuttal.

(b) The Rebuttal

The present invention, as claimed, is directed to methods of producing protein containing particles in which the protein has improved stability. The particular problems associated with protein stability in aqueous solutions are well known and described in the instant application. For example, spray drying proteins can result in materials that are thermally degraded upon processing. There can be a detrimental effect of protein degradation at the air-liquid interface of the droplets in the spray. The problems associated with protein stability can be solved by producing the protein particles according to the methods of the invention.

In contrast, Durrani is not concerned with, and does not address, the stability of any drug in any resulting spray-dried powder from Durrani's method. Even if it could be inferred that

Durrani addresses the stability of the drug, Durrani does not address the stability of a protein drug in a resulting spray-dried powder. Durrani is simply not about a method for producing spray-dried particles comprising a stabilized protein or peptide wherein the particles *consist of* the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

Durrani describes a method for direct spray-drying a drug/lipid composition to produce a powder which forms liposomes upon rehydration (*ex vivo* or *in vivo*) that is essentially equivalent to that achieved by previous methods of spray-drying a drug/lipid composition, which required the preformation of a liposome encapsulated drug suspension prior to spray-drying the liposome encapsulated drug suspension. Durrani teaches that the improved method alleviates the prior art need to preform liposome encapsulated drug suspensions while producing equivalent powders, and goes on to describe the ingredients and steps required to produce such powders. The only working examples in Durrani teach particles which include, not a protein (or a peptide), but albuterol sulfate. Durrani never addresses the issue of protein stability.

Durrani provides no suggestion, or motivation, to select specific components (and only those components) which provide improved protein stability. Given that Durrani contains no specific examples directed to particles containing proteins, the ordinarily skilled artisan does not have a reasonable expectation of success of producing protein particles with improved stability in any and all combinations of the particularly disclosed excipients, whether optional or required.

The Examiner infers that improved protein stability is an inherent result of the methods of Durrani, stating that since "Durrani discloses the same components for the spray dried particles...that the protein integrity and tap density are inherent characteristics, and would be the same as those claimed by applicant...." However, the doctrine of inherency does not apply here where the prior art products are not "identical or substantially identical". *In re Best*, 195 USPQ 430 (CCPA 1977). The products *specifically* described by Durrani are directed to powders that do not contain proteins and contain additional components that facilitate liposome formation. The products *specifically* described by Durrani (which contain small organic molecules), by definition, cannot possess improved protein stability. The products *specifically* described by Durrani contain additional excipients. Thus, the Examiner is applying the doctrine of inherency,

not to the products *specifically* described by Durrani, but those that fall within a very broad generic disclosure. The doctrine of inherency simply does not reach products that are merely generically described. The doctrine of inherency cannot be used to ignore or dismiss claim limitations which may result from the selection of only generic disclosed variables. The doctrine of inherency only applies if the result is a necessary result when the prior art is followed. There is no reason to believe that protein stability is a necessary result that is achieved by conducting each and every process generically disclosed by Durrani. Indeed, the Examiner's position is wholly inconsistent with the long and accepted practice that improvements and selection inventions that fall within the generic disclosure of a reference can support a patent.

Further, Durrani fails to teach or suggest additional claim limitations. The claims are directed to a method for producing spray-dried particles having improved stability of a protein or peptide comprising combining a protein or peptide, a phospholipid and, optionally, a buffer salt and a co-solvent or an organic solvent, and spray drying the resulting mixture to produce spray-dried particles comprising a stabilized protein or peptide wherein the particles *consist of* the stabilized protein, or peptide, the phospholipid and, optionally, the buffer salt; and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent. The claims do not allow additional components.

Durrani is interested in a method for preparing a powder which, upon rehydration, yields liposome-encapsulated drug at a comparable percent encapsulation to spray-dried preformed liposomes. All working examples presented in Durrani specifically teach particles which include, in addition to albuterol sulfate and lipid(s), other ingredients such as tocopherol, cholesterol and freon. Tocopherol is described as "a drug-protective and lipid-protective agent" (page 9, lines 20-21). These components are excluded from the present methods.

In prior Office actions, the Examiner dismisses this argument and relies upon the fact that Claim 1 of Durrani does not recite these additional excipients. Claim 1 requires that the composition contain a "lipid". The Examiner is reading more into this language than is there. It does not state that Durrani teaches compositions which consist of stabilized protein and phospholipids and an optional buffer salt. Additional excipients that facilitate liposome formation and facilitate protecting drugs and lipids are desired and preferred. There is no

teaching that good or even adequate *protein stability* can be achieved with eliminating all excipients that facilitate liposome formation and protect drugs and lipids.

In this Office action, the Examiner dismisses this argument and states that the secondary teachings overcome the omissions in Durrani. Backstrom, Edwards and Remington do not teach that it would be optional, desirable or suitable to remove excipients from a liposomal composition to improve or achieve protein stability. Backstrom and Edwards do not teach liposomal compositions at all. At best, Backstrom and Edwards teach alternative compositions suitable for pulmonary delivery. There is no apparent reason to combine these references and the Examiner has offered none.

With respect to the teachings of Backstrom, Backstrom teaches compositions which comprise a protein and an absorption enhancer. The enhancer can be a lipid, such as a fatty acid, bile salt, glycoside, cyclodextrin or a phospholipid. Column 2, lines 61-63. A preferred enhancer is sodium caprate. Phospholipids that were enhancers include only single chain phospholipids and short chain double chain phospholipids. Column 6, lines 19-40. The products are generally prepared by micronizing the protein and the enhancer, such as micronizing together (Column 9, lines 1-17). While the reference states that a solution containing both ingredients can be spray dried, the authors advise caution to avoid degradation. Column 9, lines 27-31. While additional excipients appear to be optional, the reference does not appear to specifically describe methods for stabilizing proteins. Turning to the examples, Example 1 tests a formulation comprising insulin, sodium caprate and mannitol. The product was not prepared by spray drying. As such, protein stability was not a relevant concern. No phospholipid was used. In Example 2, epithelial uptake of insulin and various lipids were tested. The formulations were not spray dried. As such, protein stability was not a concern. Long double chain phospholipids were inactive. In Example 3, hGH was tested for absorption with sodium caprate. Again, the product was not spray dried and protein stability was not a concern. No phospholipid was used. Example 4 is the only in vivo example offered by the reference. The product is micronized insulin and sodium caprate. The product was not spray dried. As such, protein stability was not a concern.

When I read the entire reference in context, I do not see where the reference states that spray drying a formulation which consists of solvent, protein, phospholipid and an optional

buffer salt would be expected to result in a stable protein formulation. Backstrom does not alone teach the claimed invention.

Further, Backstrom is not directed to liposomal formulations. Indeed, the preferred compositions of Backstrom are simple micronized admixtures of the enhancer and protein. The preferred enhancer is sodium caprate. The enhancers of Backstrom specifically exclude the long double chain phospholipids of Durrani. As such, one of ordinary skill in the art, if looking to make modifications to the Durrani formulations, would simply not turn to Backstrom. Further, neither reference, singly or collectively, teach spray dried particles consisting of stabilized protein, phospholipid and an optional salt, the claimed invention would not result, even if one were to somehow combine the teachings of these references.

Edwards teaches, *inter alia*, the pulmonary delivery of proteins, such as insulin. The particles produced by Edwards admittedly possess the preferred physical characteristics of the present invention which achieve good to excellent delivery to the lungs. The particles of Edwards can be made of a wide variety of compounds. DPPC, the preferred phospholipid of the present invention is the preferred phospholipid of Edwards. This is not surprising, given the overlapping nature of the inventive entity of the present application and the reference. Nonetheless, even Edwards does not teach that, when a protein is selected as the active agent, protein stability can be preserved by spray drying a formulation that consists of protein, phospholipid and optional buffer salt. Turning to the examples containing a protein, for example, all of the working examples employ either lactose or protamine. As such, Edwards does not teach the invention and does not provide that which is missing from Durrani and Backstrom, even assuming that it would have been obvious to combine their teachings.

Remington's adds no more to the art discussed above and clearly does not teach that which is missing from Durrani, Backstrom and Edwards. None of the references, singly or collectively, teach that spray-dried formulations consisting of stabilized proteins, phospholipids and optional buffer can be made.

As exemplified by Weiner *et al.* ("Liposomes as a Drug Delivery System", *Drug Development and Industrial Pharmacy,* 15(10): 1523-1554 (1989)) (enclosed herewith), the production and use of liposomes as a drug delivery system is a complex and distinct art with its own unique concerns and obstacles. Weiner *et al.* describe the properties of liposomes, how

liposomes are prepared and how they have been, and continue to be, adapted to efficiently and safely encapsulate a drug. Weiner *et al.* describe the various types of lipids that can be used to generate liposomes and the benefits and disadvantages of each (pages 1525-1529). Furthermore, Weiner *et al.* go on to state that "the internal or trapped volume and encapsulation efficiency greatly depends on liposomal content, lipid concentration, method of preparation and drug used" (page 1532, last paragraph). Weiner *et al.* teach the importance of cholesterol in the formation of liposomes, the encapsulation of drugs and the resulting stability of the liposomes (page 1527, first paragraph). The teachings of Weiner are consistent with the teachings of Durrani, which stresses the importance of the types of lipids used in the formulation and the addition of drug and lipid containing agents such as cholesterol and tocopherol.

The Examiner dismisses the teachings of Weiner stating that the article does not "require" that components other than phospholipids must be used and the discussion relative to cholesterol was in relation to intravenous formulations, not inhalation formulations. Please note that the mode of administration is important because of the Examiner's combination of the references. The Examiner is combining a reference which is directed to liposomes and references which describe products for inhalation. With regard to the first comment, the Examiner is reminded that the issue is whether or not the person of ordinary skill in the art would be motivated to remove all components, other than the protein, phospholipid and optional buffer salt, from the liposomal composition of Durrani with the reasonable expectation of successfully arriving at a composition with stable protein that is capable of liposomal formation upon pulmonary delivery (i.e., *in vivo* or *in situ*). Please note that Durrani teaches that the formulations can be reconstituted in advance of administration. Thus, liposomal formation can be assisted *ex vivo* by agitating the formulation where it is necessary. When a dry powder is inhaled, any liposome formation of a preliposomal powder likely occurs *in vivo*. The liposomal formation relies upon spontaneous formation. The Examiner has not shown that removing all liposome-facilitating agents will allow for *in vivo* liposomal formation in the lung. Weiner teaches that, for example, cholesterol is important to liposomal formation. Wouldn't the person of ordinary skill in the art be motivated to include, not exclude, such compounds to facilitate *in vivo* liposomal formation? Weiner's teachings are, indeed, relevant to the issue of motivation to

combine a reference directed to liposomes and references directed to pulmonary delivery of dry powders and the results one may expect upon removing excipients important to liposomal formation and stability.

With regard to the latter comment, the manner in which the liposome is administered by Weiner (injection or inhalation) is not relevant to the issue of whether or not the liposome would be expected to readily form *in vivo* in the absence of an agent that facilitates formation. If the liposome would not be expected to be formed or not be stable, it is not a desirable product as described by Durrani and its mode of administration is irrelevant. Again, Durrani teaches liposomal formulations. The person of ordinary skill in the art would not administer (by any means) a formulation according to the teachings of Durrani if it isn't, or wouldn't expect to be, liposomal. If the Examiner views Weiner as a teaching away from intravenously administered liposomal products that do not include cholesterol (to reference the Examiner's argument), then wouldn't Weiner also teach away from inhaled products that do not include cholesterol? Thus the Examiner's stated reason for refusing to consider the teachings of Weiner is without any logical basis.[2]

Durrani includes in its particles additional ingredients which materially affect the basic and novel characteristics of the claimed invention. Applicants respectfully submit that Durrani does not teach, suggest or recognize the possibility of preparing spray-dried particles consisting of a stabilized protein (or peptide), phospholipid and, optionally, the buffer salt as claimed herein.

In Claims 128-131, a buffer salt is required. Durrani specifically states that "the aqueous solution be free of phosphate salts" (page 11, line 15). As is clear from the present specification, phosphate salts are buffer salts. Accordingly, the person of ordinary skill in the art would not be motivated to add a phosphate salt, or a similar buffer salt, to the formulations of Durrani, which necessitate that the aqueous solution be "phosphate free." The Examiner dismisses the argument, as articulated in the Supplemental Brief, stating that "phosphate salts" are not required in Claims 128-131. While it is appreciated that the claims are not limited to phosphate salts, given the

[2] It is acknowledged that the claims do not require that the particles be administered via inhalation. However, it is noted that the secondary references are directed to products which are administered via inhalation. As such, the argument is certainly relevant to the motivation to combine the teachings of the references.

teachings of the reference to not use phosphate salts, the person of ordinary skill in the art would also not be motivated to employ similar salts. It is hoped that the above articulation of the argument addresses the Examiner's concern. It would be helpful to the Applicants, and perhaps the Board, if the Examiner would state whether or not a claim that limits "buffer salts" to "phosphate salts" would be considered patentable.

With respect to Claims 53 and 94, which limit the claims to human growth hormone, there is no motivation to specifically select a formulation that *consists of* hGH, a phospholipid (in an amount of at least about 10%) and an optional buffer salt, with an expectation of achieving good to excellent hGH stability. Certainly, the Examiner has pointed to none. Perhaps the Examiner is relying upon Backstrom to satisfy the missing limitations. If this is the case, the Examiner has failed to show that one of ordinary skill in the art would be motivated, with a reasonable expectation of success, to make the liposomal powders of Durrani with the hGH of Backstrom. The fact that hGH exists and is taught to be a desirable drug for delivery does not mean that the motivation to combine these references exists together with a reasonable expectation of success. Please note that the hGH of Backstrom is formulated with sodium caprate, a salt. Given the teachings against salts in Durrani discussed above, wouldn't one of ordinary skill in the art be motivated to avoid formulations which include salts? Further, the phospholipids used by Durrani are avoided by Backstrom. For example, would products produced by combining these teachings be capable of forming liposomes *in vivo*? Even if the products were in the complete absence of additional liposome facilitating excipients? Would the products be expected to retain protein stability? The Examiner has not established that the person of ordinary skill in the art would expect this to be true.

With respect to Claims 56, 57, 97, and 98, the specific stabilities to be achieved by the protein are recited. Obviously, Durrani does not teach these results. Further, the results are not an inherent feature of Durrani or spray drying. Thus, these claims are separately patentable. The Examiner relies upon Remington's to show that the tests identified in these claims are known tests. However, this does not mean that one of ordinary skill in the art would expect that the products produced by the Durrani method in the manner suggested by the Examiner would be expected to possess the stability levels set forth in the claims. Again, the Examiner is merely looking to see if the limitations presented in the claims exist in another piece of prior art. The

fact that they may (or may not) exist in the prior art does not mean that there is motivation to combine these references with a reasonable expectation of success of achieving the claimed invention.

With respect to Claims 62-64 and 102-104, the claims require a specific range of tap densities. This too the Examiner asserts, in previous Office actions, is generically taught by Durrani because Durrani does not teach any tap density at all and it is an inherent feature. Tap density is a physical characteristic of the powder. As can be seen from Durrani's examples, the physical characteristics change from run to run. Durrani's Table 2, for example, shows that some powders are sticky and some are free flowing. Example 1 of the present specification reports that the tap densities ranged between 0.02 and 0.2 g/cc. Clearly, it is not an inherent feature of the formulation alone. Thus, the Examiner's assumption is incorrect. There is no reason provided in Durrani to manufacture compositions with the specifically recited materials and the specifically recited tap densities. It is absurd for the Examiner to point to Durrani's failure to teach a claim limitation and state that it supports the rejection. Even if the Examiner asserts, improperly inferring the conclusion based upon data in the Applicants' own specification, that all spray-dried products must inherently possess a tap density of less than 0.4 g/cc (Claim 62), the evidence of record clearly establishes that this is untrue of the lower claimed tap densities. Thus, Claims 63, 64, 103 and 104 are separately patentable even from Claim 62.

Although it is not explicitly stated, it is possible that the Examiner is now relying upon Edwards to teach these limitations. If this is the case, however, the Examiner has failed to show that one of ordinary skill in the art would be motivated, with a reasonable expectation of success, to make the liposomal powders of Durrani with the physical characteristics of Edwards' particles. The fact that the physical characteristics exist and are taught to be desirable by Edwards does not mean that motivation exists to so modify Durrani together with a reasonable expectation of success and that the claimed invention would result. For example, would such products be capable of forming liposomes *in vivo*? Even if the products did not contain additional liposome facilitating excipients? Would the products be expected to retain protein stability? The Examiner has not established that the person of ordinary skill in the art would expect this to be true.

In short, none of the references, taken alone or together, teach that one may prepare a spray-dried particle consisting of stabilized protein, phospholipid and an optional buffer salt. As such, the rejection under 35 USC 103 is improper. Reversal is requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

By _____
Carolyn S. Elmore
Registration No. 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

Chelmsford, MA 01863
Dated: 9/15/4

PENDING CLAIMS

Claims 1 – 49 (Canceled)

50. (Previously Amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

51. (Canceled)

52. (Previously presented) The method of Claim 50 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

53. (Previously presented) The method of Claim 50 wherein the protein is human growth hormone.

54. (Previously added) The method of Claim 50 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

55. (Previously presented) The method of Claim 50 wherein protein stability is measured by SEC-HPLC.

56. (Previously presented) The method of Claim 50 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

57. (Previously presented) The method of Claim 50 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

58. (Previously presented) The method of Claim 50 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

59. (Previously amended) The method of Claim 50 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

60. (Previously presented) The method of Claim 50 wherein the co-solvent includes an alcohol.

61. (Previously presented) The method of Claim 50 wherein the organic solvent is present in the co-solvent in a concentration of at least 50 volume %.

62. (Previously presented) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

63. (Previously amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

64. (Previously amended) The method of Claim 50 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

65. (Previously amended) The method of Claim 50 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

66. (Previously amended) The method of Claim 50 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

67. (Previously presented) The particles produced by the method of Claim 50.

68. (Previously presented) A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 50.

69. (Previoiusly amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, and, optionally, a buffer salt, to form a mixture; and

b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

70 – 90 (Canceled)

91. (Previously amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, an organic solvent, and optionally, a buffer salt, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and, optionally, the buffer salt, and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

92. (Canceled)

93. (Previously presented) The method of Claim 91 wherein the phospholipid is selected from the group consisting of phosphatidylcholines, phosphatidylethanolamines, phosphatidylglycerols, phosphatidylserines, phosphatidylinositols and combinations thereof.

94. (Previously presented) The method of Claim 91 wherein the protein is human growth hormone.

95. (Previously presented) The method of Claim 91 wherein the protein is present in the spray-dried particles in an amount ranging from about 1 to about 90 weight %.

96. (Previously presented) The method of Claim 91 wherein protein stability is measured by SEC-HPLC.

97. (Previously presented) The method of Claim 91 wherein the spray-dried particles retain at least about 70% protein integrity when stored at about 25°C and about 60% relative humidity conditions for six weeks.

98. (Previously presented) The method of Claim 91 wherein the spray-dried particles retain at least about 50% protein integrity when stored at about 40°C and about 75% relative humidity conditions for six weeks.

99. (Previously presented) The method of Claim 91 wherein the protein is a therapeutic, prophylactic or diagnostic agent.

100. (Previously amended) The method of Claim 91 wherein the solute concentration in said mixture is at least 0.1 weight/volume %.

101. (Previously presented) The method of Claim 91 wherein the solvent includes an alcohol.

102. (Previously presented) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.4 g/cm^3.

103. (Previously amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.1 g/cm^3.

104. (Previously amended) The method of Claim 91 wherein the spray-dried particles have a tap density less than about 0.05 g/cm^3.

105. (Previously amended) The method of Claim 91 wherein the spray-dried particles have a median geometric diameter of between about 5 microns and about 30 microns.

106. (Previously amended) The method of Claim 91 wherein the spray-dried particles have an aerodynamic diameter of between about 1 micron and about 5 micron.

107. (Previously presented) The particles produced by the method of Claim 91.

108. (Previously presented) A method comprising administering to the respiratory tract of a patient in need of treatment, prophylaxis or diagnosis an effective amount of the spray-dried particles produced by the method of Claim 91.

109 – 127 (Canceled)

128. (Previously amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

129. (Previously amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and a co-solvent, said co-solvent including an aqueous solvent and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

130. (Previously amended) A method for producing spray-dried particles having improved stability of a protein comprising:

(a) combining a protein, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized protein;

wherein the particles consist of the stabilized protein, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.

131. (Previously amended) A method for producing spray-dried particles having improved stability of a peptide comprising:

(a) combining a peptide, a phospholipid, a buffer salt and an organic solvent, to form a mixture; and

(b) spray-drying said mixture to produce spray-dried particles comprising a stabilized peptide;

wherein the particles consist of the stabilized peptide, the phospholipid and the buffer salt and wherein the phospholipid is present in the particles in an amount of at least about 10 weight percent.